

GMP: Current Compliance Issues for Biologics

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Current Compliance Issues for Biologics

- CGMP Initiative
- Team Biologics
- Other Risk-Based Initiatives
- Tissue Initiatives
- Pre- and Post-Approval Inspection Issues

Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach

- FDA initiative announced in August 2002
- Two-year + program.
 - Report expected September 2004
- Applies to pharmaceuticals, including biological human drugs and veterinary drugs (excludes blood/plasma)
- Steering Committee comprised of CBER, CDER, CVM, CDRH*, CFSAN*, ORA, and the Office of the Commissioner



Summary of Objectives

- Adoption of new technological advances
- Modern quality management techniques
- Risk-based approaches
- State-of-art regulatory review and inspection policies
- Enhance consistency and coordination of FDA drug quality programs

Compliance-Related Accomplishments

To date, accomplishments include:

- 21 CFR Part 11 – Electronic Records Requirements (Final Guidance - posted 9/5/03)
 - Intend to exercise enforcement discretion with respect to:
 - Validation, audit trail, record retention, and record copying requirements of Part 11
 - Systems operational before August 20, 1997 (effective date of Part 11)
 - Intend to enforce all other provisions of Part 11
 - Withdraws earlier Part 11 guidance and Compliance Policy Guide 7153.17



Compliance-Related Accomplishments

continued

- Implementation of a Technical Dispute Resolution Process for CGMP Disputes (Draft Guidance - posted 9/3/03)
 - Domestic pilot study began 1/1/04
 - Intended to promote open, prompt discussion and resolution of scientific/technical questions and issues raised during routine biennial inspections
 - Not intended to cover disputes over procedures or administrative matters

Compliance-Related Accomplishments

continued

- Sterile Drug Products Produced by Aseptic Processing – Current Good Manufacturing Practice (Draft Guidance – posted 9/5/03)
 - Updates, clarifies, and replaces 1987 “Industry Guideline on Sterile Drug Products Produced by Aseptic Processing” with respect to personnel qualification, cleanroom design, process design, quality control, environmental monitoring, and production records

Compliance-Related Accomplishments

continued

- Comparability Protocols – Protein Drug Products and Biological Products – Chemistry, Manufacturing, and Controls Information (Draft Guidance – posted 9/5/03)
 - Guidance for use for CMC changes in approved marketing applications
 - Describes principles and procedures associated with developing and submitting comparability protocol
 - Describes consideration, development, and submission of comparability protocol and specific issues to consider for changes in manufacturing process, analytical procedures, manufacturing equipment, manufacturing facilities, container closure systems, and process analytical technology (PAT)



Compliance-Related Accomplishments

continued

- Center review of all proposed drug CGMP Warning Letters started March 1, 2003
 - CBER previously implemented review of all biological drug and device Warning Letters
- Language added to Form FDA 483
 - Clarifies that 483 items are inspectional observations and do not represent final FDA compliance determination
 - Notes that firm may discuss disagreement regarding an observation or a plan for corrective action with FDA representatives



Compliance-Related Accomplishments

continued

- Review of Team Biologics operations
- Pharmaceutical Inspectorate program established by ORA and CDER on 8/22/03
 - Highly trained individuals
 - Increased use of product specialists
 - Similar to existing Team Biologics and CBER biologics inspection practice (e.g., product specialists on inspections)



Compliance-Related Accomplishments

continued

- Developing risk-based approach for choosing sites for inspections (CDER)
 - CBER already meets statutory obligations for inspecting all licensed facilities

Team Biologics

- Implemented in 1997
- In response to reports by
 - General Accounting Office (GAO)
 - “Blood Safety, FDA Oversight and Remaining Issues of Safety”
 - February 1997
 - Office of Inspector General (OIG)
 - “Review of the FDA’s Inspection Process of Plasma Fractionators”
 - June 1997



GAO/OIG Reports

- Contained recommendations specific to the inspection of blood, blood product, and plasma manufacturers
- FDA broadened its response to include all biological products
 - “Team Biologics – A Plan for Reinventing FDA’s Ability to Optimize Compliance of Regulated Biologics Industries” (1997)
 - <http://www.fda.gov/cber/genadmin/teambio.htm>



Goals of Team Biologics

- Include the following:
 - Assure a comprehensive regulatory approach among product lines
 - Promote uniformity between CBER and the field, and among field components associated with inspections, policy implementation, and CGMP interpretation
 - Develop and maintain a highly trained and professional work force



Short-Term Outcomes

- Initially longer inspections, but timeframes now reduced
- Increase in 483 observations based on more substantive review
- More post-inspection meetings
- Increase in Warning Letters

Results

- Increased investment in facilities
- More emphasis on controlling process
- Significant increase in communication between industry and agency
- Improved consistency
- Comprehensive feedback to industry

Where Are We Now?

- Seventh anniversary
- Harmonization with CDER and CDRH
 - Stability Requirements for Licensed In Vitro Diagnostic Products (Compliance Policy Guide)
 - Guide to Inspections of Viral Clearance Processes for Plasma Derivatives
 - Revision to Requirements for Licensed Anti-Human Globulin and Blood Grouping Reagents
 - Direct Final Rule



Where Are We Now?

continued

- Ongoing efforts focused on
 - Consistency
 - Inspection timeframes

What's Next for Team Biologics?

- We are nearing completion of an in-depth evaluation – build on and improve process
 - Adopt internal quality management system
 - Develop metrics to determine impact on industry/measure success
 - Standardize training and qualifications of Core Team members
 - Risk-based work planning
 - Increased communications between headquarters and field
 - Further integration of product specialists



Relationship of Team Biologics to CGMP Initiative

- Science based
- Dispute resolution
- “Improve operations of Team Biologics”
- “Evaluate the feasibility of establishing dedicated cadres of pharmaceutical inspectors”

Additional Overlapping Areas

Team Biologics – CGMP Initiative

- Measuring success
- Quality definition
- Training of investigators
- Consistency of application of regulations
- Center review of proposed Warning Letters
 - In addition to current Office of Chief Counsel review
 - Similar to CBER existing practice



Team Biologics

Conclusions

- Team Biologics continues to evolve
- CGMP Initiative should have positive impact on efforts
- Industry can play active role

Other Risk-Based Initiatives

- Quality management systems
- Systems-based inspections
- Further development of CBER's risk-based compliance strategy

Quality Management Systems

- Design of integrated Agency-wide, risk-based quality management system
- Three working groups established
 - Framework
 - Guidance
 - Harmonization

Quality Systems Framework

- Development of framework that enhances and integrates Agency's existing quality systems
- To be implemented in Centers and field to ensure consistency of reviews and inspections
- Common vocabulary and component description
- Framework submitted to Steering Committee and adopted December 2003

Quality System Guidance Development

- Development of new educational guidance documents to encourage use of quality system principles
- First guidance expected August 2004
- CBER actively working on implementation of quality management into its programs

CGMP Harmonization Analysis

- Analyzing internal and external GMP requirements
- Review of regulations
 - 21 CFR 210 and 211
 - European Union CGMPs
 - PIC/S
 - Agency-wide CGMP regulations
- Differences noted will contribute to assessment of whether or not to revise 21 CFR 210 and 211
- Interim report presented to Steering Committee in December 2003
- Final report expected in June 2004

Systems-Based Inspections

- Compliance Program Guide: 7342.001 -
“Inspection of Licensed and Unlicensed
Blood Banks, Brokers, Reference
Laboratories, and Contractors
 - Issued July 1, 2003
 - Implemented September 1, 2003
 - <http://www.fda.gov/cber/cpg/cpg.htm>



Elements of Systems-Based Inspections

- Risk management
- Focus on critical systems
- Where applicable, provides method to determine level of inspectional coverage and resources appropriate for each inspection

Why Systems-Based Inspections?

- Ties in with Agency's risk-based initiative
- Commissioner's Strategic Plan
 - Efficient risk management
 - Improving healthcare through better information
 - Improving patient and consumer safety
 - Protecting America from terrorism
 - Smarter regulation through a stronger workforce
- Pharmaceutical CGMPs for the 21st Century: A Risk-Based Approach

Why Systems-Based Inspections?

continued

- More focused inspections
 - Identify and train investigators on:
 - Critical systems
 - Critical issues within the systems
 - Specific technical training

Why Systems-Based Inspections?

continued

- Best Use of Resources
 - Reduce inspection length
 - Use resources to conduct more inspections, develop guidance, etc.
 - Optimize level of effort necessary to determine compliance

CBER Compliance Plans

- Additional CBER initiatives
 - Systems-based Source Plasma Compliance Program Guide
 - Systems-based Biological Drug Compliance Program Guide
 - Allergens, vaccines, plasma derivatives, and therapeutic drugs
 - Future tissue compliance program update following implementation of tissue final rules



CBER Compliance Plans

continued

- CBER is reviewing the lot release process from a risk-management viewpoint
 - Review of current testing matrix
 - Compare to other regulatory agency models
 - Pilot program for plasma derivatives to implement PDUFA-like timeframes
- Improvements to the review process
 - Developing review templates for greater standardization
 - Reviewing current guidance for changes to be reported using a risk-based approach



Tissue Initiatives

- Human Cells, Tissues, and Cellular and Tissue-Based Products; Establishment Registration and Product Listing
 - Final Rule published January 19, 2001
 - Creates a unified registration and listing system for establishments that manufacture HCT/Ps

Tissue Initiatives

continued

- Eligibility Determination for Donors of Human Cells, Tissues, and Cellular and Tissue-Based Products
 - Final Rule and Draft Guidance published May 20, 2004
 - Rule effective May 25, 2005
 - Part of comprehensive new system of regulation for human cells, tissues, and Cellular and Tissue-Based products (HCT/P's)

Tissue Initiatives

continued

- Donor Eligibility Rule (continued)
 - Extends scope of communicable disease regulation beyond conventional and eye tissues, to reproductive tissues, dura mater, heart valves, cellular therapies, and other medical products containing cells and tissues
 - Requires screening and testing of donors for additional communicable disease risk factors.
 - Updates communicable disease agents and diseases of concern (e.g., TSE and HTLV) and allows flexibility and rapid initiation of screening and testing for newly emerging or recognized diseases (e.g., sepsis and West Nile Virus)
 - Contains requirements for written SOPs and relating to record-keeping, quarantine, storage, and labeling

Tissue Initiatives

continued

- Current Good Tissue Practice for Manufacturers of Human Cellular and Tissue-Based Products; Inspection and Enforcement
 - Proposed Rule published January 19, 2001
 - Publication of Final Rule anticipated soon
 - Would require controls to prevent infectious disease contamination when tissues are recovered, received, stored, processed, and distributed
 - Would require submission of adverse event and product deviation reports
 - Would include inspection and enforcement provisions to monitor and enforce compliance



Pre-Approval Inspection Issues

- Manufacturing deficiencies continue to hinder speedy approvals
- Some issues observed more often than others
- Greater attention to these issues could prevent delays

Pre-Approval Inspection Issues

continued

- Quality Agreements (contract manufacturers)
 - Change control system does not include notification of applicant and/or direct involvement of applicant in implementation decision
 - Example: Introduction of an investigational product

Pre-Approval Inspection Issues

continued

- Process Validation/Manufacturing Consistency
 - Not performed and/or completed prior to inspection
 - Consistency in manufacturing not demonstrated
- Equipment and Systems Qualifications
 - Not done at all
 - In-progress
 - Did not include critical parameters

Pre-Approval Inspection Issues

continued

- Quality Control Oversight
 - Inadequate investigation of deviations
 - Inadequate and incomplete corrective and preventative actions
- Standard Operating Procedures
 - Not capturing actual practice
 - Lack of SOP

Post-Approval Reviews

Hot Topics

- Under-reporting of changes in annual reports and implications for released and distributed products
 - When unsure, verify reporting category with CBER
- Submission of supplements for changes that have not been implemented [excluding comparability protocols under 21 CFR 601.12(e)]
 - Changes should be implemented with relevant data collected to assess impact of change on the product(s)



Post-Approval Reviews

Hot Topics - continued

- Incomplete supplements being received
- Changes reported in supplement utilize novel validation approach, which may not be consistent with regulatory expectations
 - When planning a change using a matrix, bracketing, or “family” approach, recommend discussions with CBER on adequacy of approach prior to final protocol development

Warning Letter Citations FY01-04*

- Very consistent year-to-year
- May relate to failure to determine and correct root cause

* Through 5/1/04



Warning Letter Citations FY01-04*

continued

- Failure to implement corrective/preventive action or conduct a thorough investigation
 - 21 CFR 211.192
 - 21 CFR 820.100
- Examples
 - Repeated test failures not investigated
 - Inadequate investigation of failed particulate inspection

* Through 5/1/04



Warning Letter Citations FY01-04*

continued

- Failure to establish and/or follow adequate written procedures
 - 21 CFR 211.100
- Examples
 - SOPs not followed
 - SOPs inadequate
 - SOPs not established

* Through 5/1/04



Warning Letter Citations FY01-04*

continued

- Failure to properly test prior to release for distribution
 - 21 CFR 211.165
- Examples
 - Assays used in release-testing not validated
 - Retesting conducted but not addressed in SOP

* Through 5/1/04



Warning Letter Citations FY01-04*

continued

- Failure to implement testing program to assess stability characteristics of product
 - 21 CFR 211.166(a)
- Examples
 - Stability potency tests not completed on schedule
 - Inadequate data to demonstrate sterility of components/product at end of shelf life

* Through 5/1/04



Information and Contacts

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